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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475	11/04/1998	ANNIE FONG	238/046	1830

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/28/2003 17

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/186,475	Fong et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Nov 21, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Oct 1, 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*

Claim(s) objected to: *none*

Claim(s) rejected: *1-3, 5-11, 16-18, 23, 24, and 28-31*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

Susan Ungar

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

1. The Amendment-After-Final filed November 21, 2002 (Paper No. 16) in response to the Office Action of May 21, 2002 (Paper No. 14) is acknowledged and has been entered. Previously pending claim 15 has been canceled.

Claim Rejections - 35 USC § 112

2. Claims 1-3, 5-11, 16-18, 23-24, 28-31 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 14, Section 4, pages 3-5.

Applicant argues that (a) the markers recited in present claim 1 is enabled within the disclosure of the present application wherein the Examiner's attention is directed to the description on pages 23-26, in particular pages 24-25 drawn to other markers, (b) Applicant cites case law, *In re Wright, In re Marzocchi, Hybritech Inc. V. Monoclonal Antibodies, Inc.*, and argues that the Office improperly shifts the burden to Applicants to positively prove enablement rather than recognizing Applicants' presumption of enablement and that undue experimentation is not required to practice the claimed invention.

The arguments have been considered but have not been found persuasive because (a') a review of the cited support shows that the support is rife with uncertainties, for example, p. 24, line 24 "CD40 may be related to angiogenesis", p. 24, line 25 "suggest a role for the plasminogen activation system in tumoral angiogenesis". Further, p. 25, lines 9-14 are drawn to t-PA which is released from endothelial cells and whose high expression level correlates with poor outcome, there is not even a suggestion that the marker is associated with angiogenesis. Although the specification states that ETS-1 regulates the expression of certain

genes and that it plays an important role in angiogenesis apparently because it regulates the expression of proteases, it does not appear that a direct correlation to angiogenesis such that its expression can be used as specifically claimed, has been established for the reasons of record, (b) Examiner presented sound scientific reasoning as well as published guidelines on factors for determining drug dosage. Although Applicant cites support in the specification and cites case-law, it is noted that Applicant does not argue that Examiner is incorrect in the finding that the invention is not enabled because the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate with angiogenesis of that the state of the art is complex and unpredictable. Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

3. Claims 1-3, 5-6, 9-11, 16-18, 23-24 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 6, pages 6-7.

Claims 1-3, 5-11, 16-18, 23-24, 28 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 7, pages 8-9.

Claims 1-3, 5-11, 16-18, 23-24, 28 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 8, pages 9-11.

Claims 1-3, 5-11, 16-18, 23-24, 28-31 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 9, pages 11-12.

Since Applicant argues all of the rejections under 35 USC 103 first paragraph together, the response to all of the rejections will likewise be done.

Applicant argues that (a) Applicant has failed to establish proper motivation or a reasonable expectation of success. The argument is drawn in particular, Ullrich and Tang, each of which relate to FLK-1 and VEGF and Mandriota which relates to u-PA wherein Examiner has failed to establish a proper motivation to combine or provided a bases for a reasonable expectation of success, (b) Examiner relies on at least four references, at best using Applicant's disclosure as a blueprint and therefore using impermissible hindsight vision, (c) Ullrich fails to teach or fairly suggest monitoring markers or suggest monitoring of u-PA, while Mandriota discloses u-PA increases with VEGF, this reference fails to disclose a method of determining an efficacious dose to a subject for the purpose of modulating angiogenesis comprising monitoring u-PA and the other references fail to cure these deficiencies.

The arguments have been considered but have not been found persuasive because (a') as previously set forth, Tang et al specifically teach a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis, as previously set forth Ullrich teaches known markers (VEGF and flk-1) used to monitor cancer in patients wherein, as taught by Mandriota, u-PA is increased in blood cells in response to VEGF. Examiner provides a nexus between the known markers and u-PA and clearly provides motivation for the combination for the reasons previously set forth, (b') in response to applicant's argument that the examiner's conclusion of obviousness is based upon

improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981), (c')Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). Applicant's arguments have not been found persuasive and the rejection is maintained.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER